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(19)

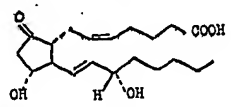
(54) STABLE SOLUTIONS AND COMPOSITIONS COMPRISING PROSTAGLANDINS

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

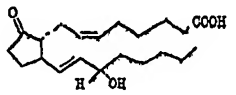
This invention relates to a method of dispensing PGE_2, or a racemate thereof, for enteral or parenteral administration, especially for intravenous infusion, which comprises preparing a concentrated stock solution of the PGE_2 in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent, sterilizing the solution when intended for parenteral administration, storing the stock solution at a temperature low enough to prevent excessive dehydration, and prior to administration, diluting said stock solution into a liquid or solid vehicle.

The invention also relates to a stable, concentrated solution of such PGE_2 in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent suitable for dilution into a liquid or solid vehicle, especially such solutions that contain not more than 0.1% water.

PGE_2 has the formula



It is effective for inducing labor or for effecting therapeutic abortions. It is unstable, however, and tends to run down by dehydration to PGA_2 which has the formula



It has been necessary, therefore, to store PGE_2 and stock solutions thereof at very low temperatures, for example minus 20°C. or lower, to minimize dehydration to PGA_2.

It has now been found that this tendency of PGE_2 to run down, due to dehydration to PGA_2 on storing in solution, can be deterred using an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent to prepare a stock solution. Stock solutions of PGE_2 so prepared, i.e., in a pharmacologically-acceptable, anhydrous, water-miscible, dipolar aprotic solvent, for example, anhydrous N,N-dimethylacetamide, can be stored at relatively high temperatures, for example, up to 25° or so, depending upon the solvent and the water content thereof, for relatively long periods of time, for example, 1 year, without excessive run down due to dehydration to PGA_2. Such solutions, therefore, when sterilized, for example, by filter sterilization provide a satisfactory method for dispensing PGE_2 for administration parenterally, for example, by sterile infusion or by injection into the amniotic sac, or when not sterilized for dilution into water for enteral administration or into lactose tablets or suppository base for intravaginal administration.

PGE_2 as used herein refers to parenteral grade PGE_2, i.e., PGE_2 sufficiently pure for parenteral administration (U.S. Patent 3,598,858). Even this pure material is subject to run down showing that dehydration is an inherent characteristic of the compound.

While anhydrous N,N-dimethylacetamide is given by way of illustration, it is to be understood that other pharmacologically-acceptable, dipolar aprotic solvents can be used. Other suitable dipolar aprotic solvents are tetramethylurea, hexamethylphosphoramide, dimethylsulfoxide, sulfolane, acetone and isiopropyl methyl ketone. The dipolar aprotic solvents, especially N,N-dimethylacetamide, have great solvent power for PGE_2 and, moreover, give very stable solutions.

By water-miscible is intended those solvents which mix with water in all proportions

[Price 25p]

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or which are so highly soluble in water that they behave as if they were completely miscible.

It is desirable that the solutions according to the invention be relatively concentrated, i.e., concentrated relative to the effective concentration, i.e., the concentration at which the drug is used. Thus with N,N-dimethylacetamide or dimethylsulfoxide, or like dipolar aprotic solvent, the concentration could be as high as 100 m.g/ml. or so. Ordinarily it will be sufficient if the solute is present in at least about 1 mg. per ml. Such solutions, though seemingly dilute, are relatively quite concentrated with respect to the effective concentration.

It is to be understood that pharmacologically-acceptable members to the liquid or solid vehicle to be administered rather than on the stock solutions itself. Some anhydrous solvents, for example, might not be pharmacologically-acceptable undiluted as in the stock solution but is very much so when diluted with a large volume of water as in enteral or parenteral administration or when diluted into a lactose tablet or suppository base for intravaginal administration. For example, 1 ml. of a 50 mg./ml. solution of PGE_2 diluted into 1 liter of infusion solution gives a solution containing 0.005% PGE_2. At the same time the concentration of the solvent, 0.1%, is well below that safe for intravenous infusion. Thus a pharmacologically-acceptable solvent as used herein is one which on dilution into the liquid or solid vehicle causes no untoward pharmacodynamic effect.

An anhydrous solution is to be considered as one containing not more than 0.5% V/V of water. All commercially available solvents contain water. Ordinary "pure" N,N-dimethylacetamide may contain up to about 0.5% water whereas "spectrograde" N,N-dimethylacetamide may contain as little as 0.3% water. An anhydrous solvent, therefore, is to be considered as one containing not more than about 0.5% water. The Karl Fischer method can be used to determine the water content.

The formula given above for PGE_2 is stereospecific. It designates the naturally occuring form identified in U.S. Patent 3,598,858. Synthesis of PGE_2 sometimes gives a racemic mixture of PGE_2 and its mirror image. It is not necessary to isolate the PGE_2 from such racemic mixtures. Such mixtures are therefore within the scope of the invention.

The invention can now be more fully understood by reference to the following examples in which the parts and percentages are by weight and the units in the C.G.S. system unless otherwise specified.

EXAMPLE 1

Parenteral grade PGE_2 is dissolved in anhydrous N,N-dimethylacetamide containing 0.4% water (determined by the Karl Fischer method) in the proportions of 5 mg. PGE_2 for each ml. of anhydrous N,N-dimethylacetamide. The solution is then filtered sterile by passing it through a microporous (solvent-resistant) filter, e.g., Millipore (Registered Trade Mark) Solvinert 0.25 microns or Gelman Metricel Alpha-8 0.2 microns aseptically packaged in 1 ml. quantities in sterile ampoules and kept under refrigeration at not more than 5° until neede. At that time the contents of one ampoule (1 ml.) are diluted into 1 l. of infusion solution and administered intravenously at the rate of 5 mcg. of PGE_2 per minute. This regimen is intended for therapeutic abortion.

EXAMPLE 2

Parenteral grade PGE_2 is dissolved in spectrograde N,N-dimethylacetamide (0.1% water) in a concentration of 10 mg. per ml. The solution is filter sterilized as in Example 1 and packaged aseptically in 0.5 ml. quantities in sterile ampoules. This solution can be stored at room temperature. It is administered in the same way and for the same purposes as in Example 1.

EXAMPLE 3

Parenteral grade PGE_2 is dissolved in anhydrous N,N-dimethylacetamide (0.1% water) in the proportions of 0.75 mg. PGE_2 to 1.5 ml. anhydrous N,N-dimethylacetamide. The solution is then filter sterilized as in Example 1, aseptically packaged in 1.5 ml. quantities in sterile ampoules, and kept under refrigeration at not more than 5° until needed. It is administered by diluting the contents of 1 ampoule (1.5 ml.) into 150 ml. of infusion solution and administered intravenously at the rate of 0.5 mcg. of PGE_2 per minute. This regimen it intended for including labor.

WHAT WE CLAIM IS:—

1. A solution of PGE_2, or a racemate thereof, in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent in a concentration of at least 1 mg.. per ml.

2. A solution according to claim 1 in which the solvent in anhydrous N,N-dimethylacetamide containing not more than 0.1% water.

3. A solution according to claim 2 which is sterile.

4. An aseptically packaged sterile unit dose in the form of an ampoule comprising a filtered sterilised solution of PGE_2 or a racemate thereof in an anhydrous water-miscible, pharmacologically-acceptable, dipolar aprotic solvent in a concentration of at least 1 mg per ml.

5. A therapeutic composition as claimed in claim 1 comprising a filtered sterilised solution of PGE_2 or a racemate thereof in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent in a concentration of at least 1 mg per ml together with a sterile diluent miscible therewith.

6. A therapeutic composition comprising PGE_2 or a racemate thereof substantially as herein described with reference to the Examples.

7. A therapeutic composition as claimed in claim 6 and in ampoule form.

For the Applicants:
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancery Lane,
London, WC2A 1HN.

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